

Laboratory Interpretation

Introduction

The complete blood count (CBC) and coagulation studies (coags) are commonly obtained laboratories. They are considered screening labs—no clinical reasoning requires them. Therefore, these labs need interpretation on a routine basis. There is no reason to refer to a hematologist if one of the numbers is out of normal range (one dean of a medical school who is also a practicing hematologist loves to tell the story of the referral to an academic subspecialty clinic for a WBC of 13 without symptoms). If you aren't giggling right now, it's OK. The absurdity of that story will be apparent by the end of this lesson. This lesson is about putting scary lab test interpretation in its place, and giving you some test-taking strategies at the same time.

You won't come out of this lesson with many actionable items. The purpose is to demystify “how complex” hematology is. Because the CBC and the coagulation studies report so many values, and because students are intimidated by interpretation of a blood smear, students freak out over “the blood tests.” We're going to show you some knee-jerk reactions you should have when you see a value out of range, give some clinical pearls to help solidify the specific details, and then show you that the numbers on the CBC correspond to the color and shape of the cells on smear, effectively telling you the same thing twice.

Remember that blood smears are like X-rays. The interpreter **cannot give you a diagnosis** based on a single test. Just as the radiologist reports “infiltrate” on the X-ray, which means “some lighter grey stuff in the spot I expected darker grey stuff” and not “pneumonia,” so too is the blood smear insensitive and rarely pathognomonic. If the X-ray was ordered on a patient with CHF exacerbation, the infiltrate is likely to be fluid. If the X-ray was ordered on a patient with fever, cough, and productive sputum, the infiltrate is likely to be pneumonia. The radiologist doesn't report a diagnosis, but findings. See the blood smear and the hematologist (or pathologist) as the same thing as an X-ray and radiologist. The interpreter will report findings on the blood smear but won't give you a diagnosis. That being said, **on a licensing exam**, if given a blood smear, **the blood smear contains the answer**. Specifically, with *Plasmodium* species (ringed trophozoites, schizonts), babesiosis (Maltese cross), and sickle cell disease (sickled cells).

So, with that, we're going to review different lab results, what they mean, and what you should do, and then review classic blood smears and list the conditions they are associated with. Not because we believe in this kind of teaching, but because you will get questions about them on the test. And if we get this lesson out of the way up front, we can focus on the things you are supposed to learn, the way you are supposed to learn them—in the context of the Clotting, Anemia, and Proliferation series. You'll already have been exposed to this material, and will demonstrate that familiarity when it counts.

The Complete Blood Count and the Coagulation Panel

The complete blood count (CBC) is a measure of the cells of the bone marrow. The bone marrow makes leukocytes (WBCs), erythrocytes (RBCs), and thrombocytes (platelets).

Platelets and factors are almost always discussed together as a unit, throughout this course, because platelets start clotting while factors finish it off. So, even though the complete blood count has the platelets (because the CBC assesses hematopoiesis and bone marrow) and the coagulation panel monitors the factors (indirectly), we want you associating the platelets with the coagulation panel.

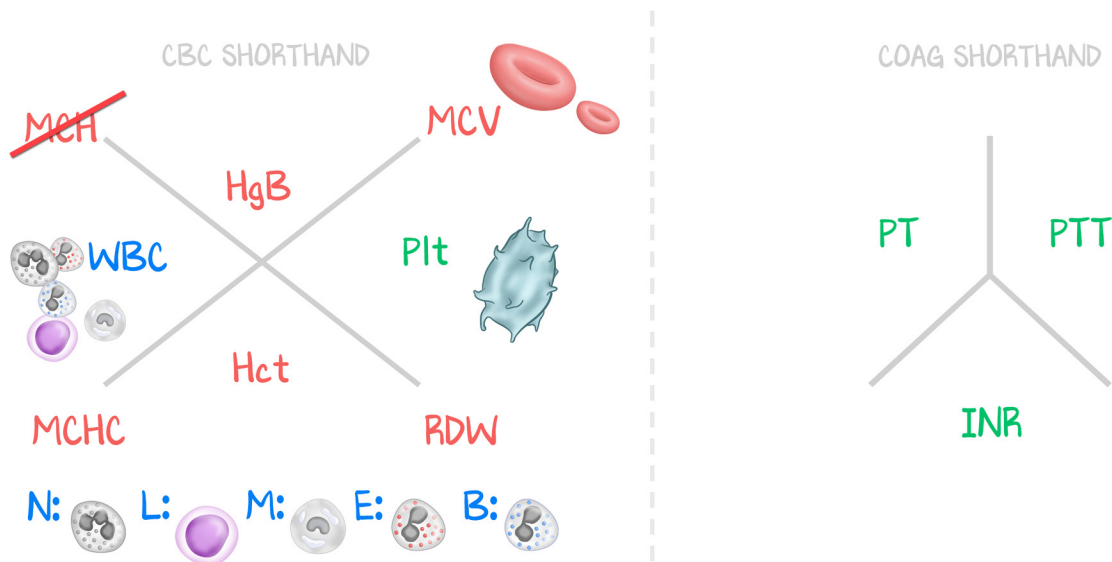


Figure 2.1: Hematology Laboratory Shorthand

This is a color-coded data-tracking method. The white blood cell count and differential are in blue. The red blood cell indices are in red. The platelets and clotting are in green. The utility of this shorthand “stick method” may not yet be apparent, but it will become second nature in clinicals. By the end of this course, you will be unable to separate the diseases and dysfunctions from the elements of this shorthand.

When it comes to disorders of the CBC, if ever a definitive diagnosis is required, a **bone marrow biopsy** is usually the best test. Best test doesn’t mean the test to do. What you’ll see is that bone marrow biopsies are done to prove a cancer in the marrow, and other diagnoses are made without the biopsy.

Interpretation of WBCs

A normal WBC range is 4–12 (thousand). A **low WBC** count is called **leukopenia**. A **high WBC** count is called **leukocytosis**. Leukocytes are all white blood cells. You should be concerned when the WBC count closes in on 1. In particular, when the **absolute neutrophil count (ANC)** drops below 1,000, the patient is said to be **neutropenic** and is at risk of severe, life-threatening infections. The absolute neutrophil count is not reported directly. Instead, you must look at the differential. When reporting an ANC, say the complete number, as in 1,250, not 1.2.

The **differential** gives you the percentage of each leukocyte. The normal values are 80% neutrophils, 10% lymphocytes, 5% monocytes, and some small number of eosinophils and basophils. The absolute neutrophils is calculated by multiplying the percent neutrophils against the total leukocyte count. You could do this exercise with lymphocytes, monocytes, etc., but these are not clinically relevant. A WBC of 4,000 and 80% neutrophils is 3,200 neutrophils ($4,000 \times 8 = 32,000$; remove a zero = 3,200).

The differential matters more when the values are elevated.

-CYTES ARE CELLS	-PHILS ARE GRANULOCYTES, SPECIALLY NAMED CELLS
Leukocyte, leukocytosis, leukopenia	Neutrophil, neutrophilia, neutropenia
Lymphocyte, lymphocytosis, lymphopenia	Eosinophil, eosinophilia, eosinopenia ← not said often
Monocyte, monocytosis, monocytopenia	Basophil, Basophilia

Table 2.1: Saying It Right, White Blood Cells

Note that words ending in -cyte, when they elevate, demonstrate a -cytosis; elevation of words ending in -phil demonstrates a -philia. All white-blood-cell words, when low, demonstrate a -penia.

Neutrophilia (increased neutrophil count) can be a signal of any number of things. Neutrophils are fully differentiated from their immediate precursor, the band cell. Neutrophilia (many neutrophils) **with bandemia** (many neutrophils, some of which are bands) indicates a **bacterial infection**. An increase in neutrophil count without bandemia may still be a bacterial infection, but can also be a distractor. The white blood cell count can go up with glucocorticoids, for example. But a **left shift**, defined by the excess production of neutrophils that results in immature versions of those neutrophils being released (called band cells), indicates infection. A neutrophil count greater than 25 should initiate investigation for *C. diff* colitis, an abscess, or myelogenous leukemia. A one-time lab value does not warrant a bone marrow biopsy, but persistent elevation that high means something is very, very wrong.

Lymphocytosis (elevated lymphocyte count) is associated with acute viral infection when the WBC is relatively normal and the percent lymphocytes increased. Severe increases in the lymphocyte count (the number associated with this phrase you should not yet know) are indicative of a lymphocytic malignancy. It is the subject of much of the Proliferation series.

Peripheral **eosinophilia** (elevated levels of eosinophils), detected as being greater than 10% on the differential, is associated with the NAACP—Neoplasm, Allergy/Asthma/Atopy, Autoimmune, Collagen vascular disease, Parasites.

Basophils and monocytes have little impact and the numbers do not telegraph disease or differential.

Further evaluation of leukocytes can be performed with a blood smear or flow cytometry. **Blood smears** can look for **blasts** in peripheral circulation. Blasts in the blood means **cancer**. There are also specific types of leukocytes, usually artifacts of the preparation, that are markers for a specific disease. The Downey cells of EBV infectious mononucleosis are an example. Do not learn a list of white blood cell findings correlated to their diagnoses. Learn each finding in context of the diagnosis, learning the illness script for the disease, not the white cell finding.

Flow cytometry (“flow,” colloquially) can work for any cell that is in the blood that has CD markers. You will see it used to evaluate for a hemolytic disease (therefore being used on something other than WBCs), but you should associate flow cytometry with WBCs. You can’t tell T cells apart from B cells under the microscope. You can with flow cytometry. All cells have proteins in their plasma membrane. The proteins that flow cytometry targets to identify cells are called **cluster of differentiation (CD)** markers. Cells express CD markers. We manufacture antibodies tagged with fluorescence that bind specifically to the CD marker. We take a sample of cells. We add to that sample two antibodies. Each antibody is to a specific CD marker and tagged with a fluorescence. Any cell with the CD marker that antibody targets will have the antibody firmly attached to that cell, and will fluoresce the color of the tag. The entire sample is run through a laser, each cell in single file. The laser will refract according to which antibody is present on that cell. The computer measures the fluorescence intensity and produces a scatter plot, informing the technician how many cells in the sample were tagged by an antibody. In Figure 2.2 we have removed the numbers which add confusion and added the + and – symbols to the interpretation, and is how you should think of flow cytometry reports.

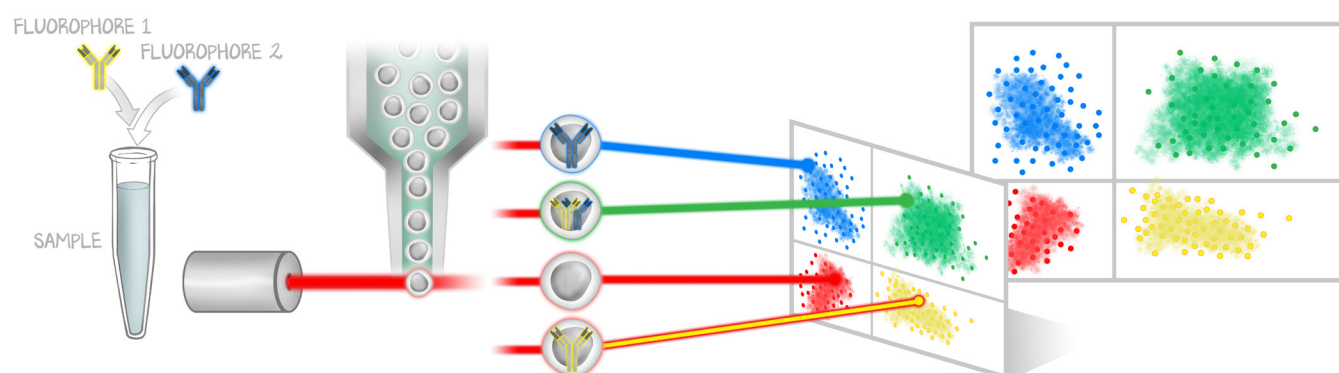


Figure 2.2: Flow Cytometry

In this case, there are four phenotypes of cells—those in the lower left quadrant that are neither CD3-positive nor CD8-positive, those in the upper left quadrant that are CD3-positive but CD8-negative, those in the lower right quadrant are CD8 positive but CD3 negative, and those in the right upper quadrant, which are both CD3-positive and CD8-positive.

All cells other than lymphocytes have a definitive shape, size, and characteristic nucleus (Immunology #2: *Taxonomy of Immune Cells*). Lymphocytes look like lymphocytes but only flow can tell the difference between B cells and T cells. Start with CD4 T-helper cells and CD8 cytotoxic cells. You learned in Immunology that these cells express the TCR and CD3. Notice anything about those CD numbers?

T cells have single-digit CD markers. B cells' typical CD markers are CD19 (during development), then CD20, CD21, and CD22 (as mature cells). **B cells have double-digit CD markers near 20.** The only exception is that TdT, expressed in very early stages of both T-cell and B-cell maturation, is CD10.

T cells CD3, 4, and 8; B cells CD19, 20, 21, and sometimes 10.

T-CELL CD MARKERS	B-CELL CD MARKERS	OTHERS
CD3	CD10	RBCs with paroxysmal nocturnal hemoglobinuria are CD55- and CD56-negative
CD4	CD19	Hodgkin's lymphoma are B cells with CD15- and CD30-positive, others negative
CD5	CD20	Hematopoietic stem cell of bone marrow CD34
CD8	CD21	
CD10	CD22	

Table 2.2: CD Markers

Interpretation of RBCs

Some folks are hemoglobin people; others are hematocrit people. Hemoglobin is the physiologic mechanism by which oxygen is delivered, and you have to learn how hemoglobin works. We advocate for abandoning the hematocrit as a thing, sticking with the molecule in red blood cells as your frame of reference, hemoglobin. Hemoglobin times three is hematocrit, so if you have an attending who is a crit person, you can easily adapt. If the **hemoglobin is low**, that is **anemia**. If the hemoglobin is high, it is **polycythemia**. Polycythemia must be separated into malignancy (low EPO, yet lots of RBCs) and reactive (high EPO, therefore lots of RBCs).

The **red blood cell indices** are numeric representations of the **size** and the **color** of the blood smear.

The **mean corpuscular volume** (also mean cell volume, or **MCV**) describes how big, on average, the cells are. That's **ON AVERAGE**. The MCV is super useful and is how we will teach you to approach anemia—too small (< 80), too large (> 100), or normal (80–100). On its own, the MCV does nothing for the diagnosis, but does help narrow your differential. The pathologist will do this as well when she looks at the smear—“these are small, medium, or large”—and call them microcytic, normocytic, or macrocytic. The **RDW**, the red blood cell distribution width, measures how much variation there is around that average. If the RDW is small, then all the cells are that size. If the RDW is large, then there is a lot of variation.

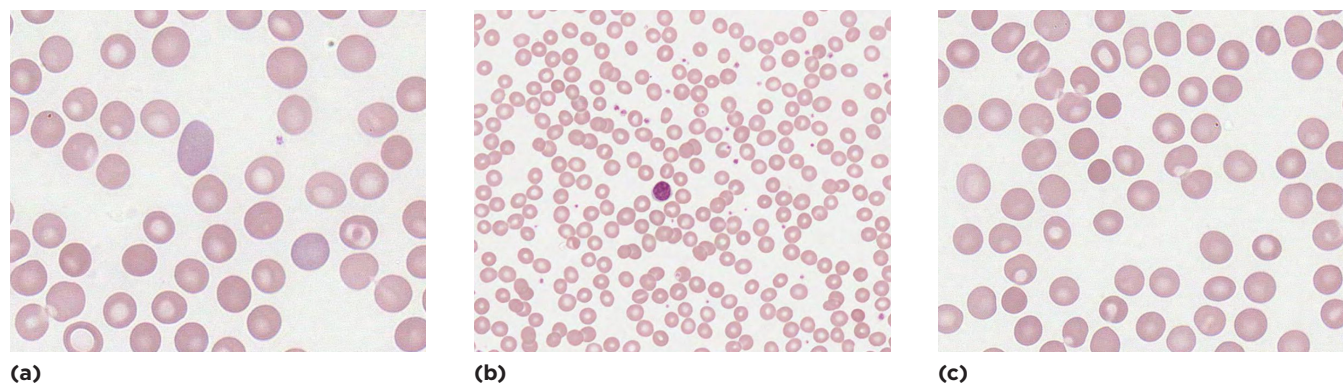


Figure 2.3: Red Blood Cells

(a) Macrocytes next to a normal red blood cell. (b) Microcytes next to normal red blood cells. (c) Spherocytes amongst normal RBCs.

The mean hemoglobin content (MHC) is an automated test necessary for calculating a useful index; never use the MHC yourself. The **mean corpuscular hemoglobin content** (MCHC) is how much hemoglobin is in each cell, adjusted for how big the cells are (MHC/MCV). To call it a “useful index” gives the MCHC a lot more credit than it deserves, when compared to the MCV. However, a high MCHC either means the cells are small or they have more hemoglobin than usual. Since “more hemoglobin than usual” isn’t a pathologic state, an elevated MCHC implies **smaller, concentrated cells**—small cells with a normal hemoglobin. This is seen in **spherocytes** (hereditary spherocytosis, autoimmune hemolytic anemia). The thing is, if you have the smear, you will just look at the slide and **SEE SPHEROCYTES**. Spherocytes are identified by being spherical (circles on the smear) with no central pallor. No central pallor means they are, on average, darker than normal cells. **Darker is hyperchromic** and is the same thing as an **elevated MCHC**. Lighter, therefore, is hypochromic and is the same thing as a decreased MCHC, as is seen in conditions of deficient hemoglobin (all production anemias).

Pathologists like to combine words to imply what the diagnosis could be. “Hypochromic microcytic smear” means small cells (low MCV) and low hemoglobin even relative to their small size (low MCHC). “Hypochromic microcytic” sounds so technical! It must describe a specific condition! While it is commonly associated with iron deficiency anemia, all slow production anemias can be hypochromic and microcytic, meaning that “hypochromic microcytic” does nothing more for you than “a low MCV” does.

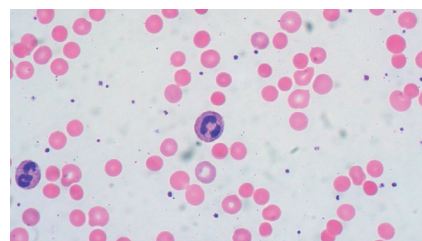
The **shape** is the only thing you can get from a smear that you cannot get from the numbers. Rather than walk through each one, we’re going to give you the summary table and examples now, then engage the smears specifically when we get to the disease they are associated with in *Anemia #7: Normocytic Anemia*. While not pathognomonic in life, when provided a blood smear on a licensing exam, the answer is generally contained in the smear.

SUGGESTIVE			
SPHEROCYTES	TARGET CELLS	SCHISTOCYTES	DACROCYTES
Hereditary spherocytosis	Hgb C	MAHA	MDS
AIHA	Asplenia	Mechanical heart valves	Fibrosis
	Liver disease		
	Thalassemia		Thalassemia

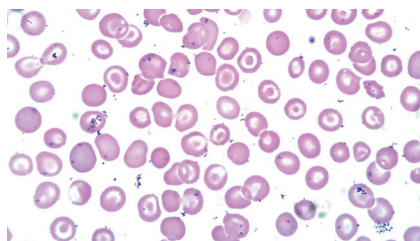
Table 2.3: Suggestive Blood Smear Findings

DIAGNOSTIC			
RINGED TROPHOZOITES	SCHIZONTS	MALTESE CROSS	SICKLED CELLS
<i>Plasmodium</i>	<i>Plasmodium</i>	Babesiosis	Sickle cell disease

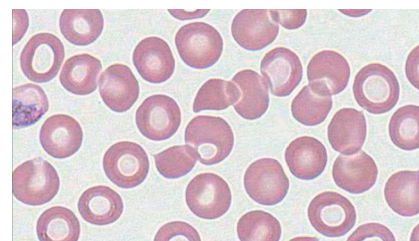
Table 2.4: Diagnostic Blood Smear Findings



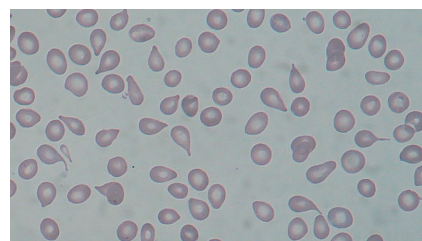
(a)



(b)



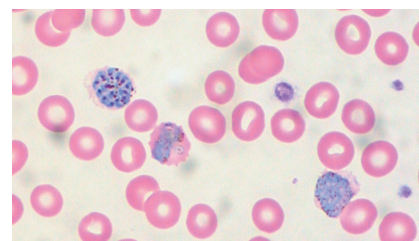
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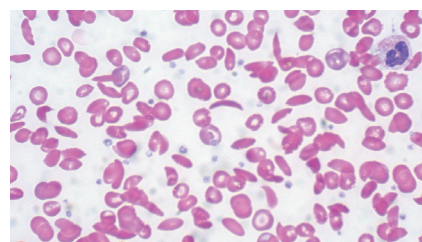
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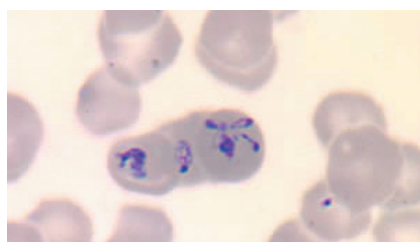
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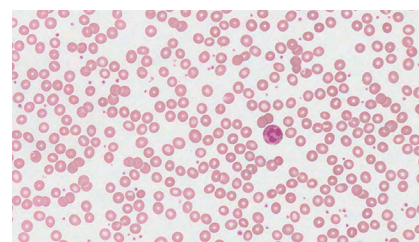
(f)



(g)



(h)



(i)

Figure 2.4: Blood Smears

A display of commonly tested blood smears. This is meant merely as an introduction. We'll get into the specifics when they are relevant throughout the module. (a) Spherocytes. (b) Target cells. (c) A schistocyte. (d) Dacryocytes. (e) Ringed trophozoite. (f) Schizont. (g) Maltese cross. (h) Sickled cells. (i) Normal blood smear for comparison.

Interpretation of Bleeding—Platelets and Factors

In Clotting #1: *Hemostasis* we will absolutely separate your thinking into primary hemostasis (platelets, CBC) and secondary hemostasis (factors, coags). We'll show you how to clinically reason your way to needing only one test, but we also want you doing the right thing for your patient when the time comes to act—when you see a patient with hemorrhage, get both the CBC and the coags.

The CBC gives you the platelet count. Normal is 120–400 (thousand). **Thrombocytopenia** (low platelets) increases the risk for bleeding, and bleeding in this condition takes longer to stop. Platelets can also be in normal number but be defective, as in the administration of antiplatelets such as aspirin or clopidogrel (Clotting #3: *Clotting Pharmacology*), so a normal platelet count does not rule out platelet problems. In hospitalized patients who are acutely ill, you will commonly encounter double-digit platelets, where the patient lives, with no meaningful compromise to their life or daily function. When the platelets get below 50, we worry about hemorrhage. When they get below 10, spontaneous intracranial hemorrhage is possible. When the platelets are this low, give platelets. **Thrombocytosis** is increased number of platelets. If the number is high, it is likely to be dehydration, hemoconcentration falsely increasing the reported number. If it is real, thrombocytosis is usually cancer related (Proliferation #2: *Myeloproliferative Disorders*).

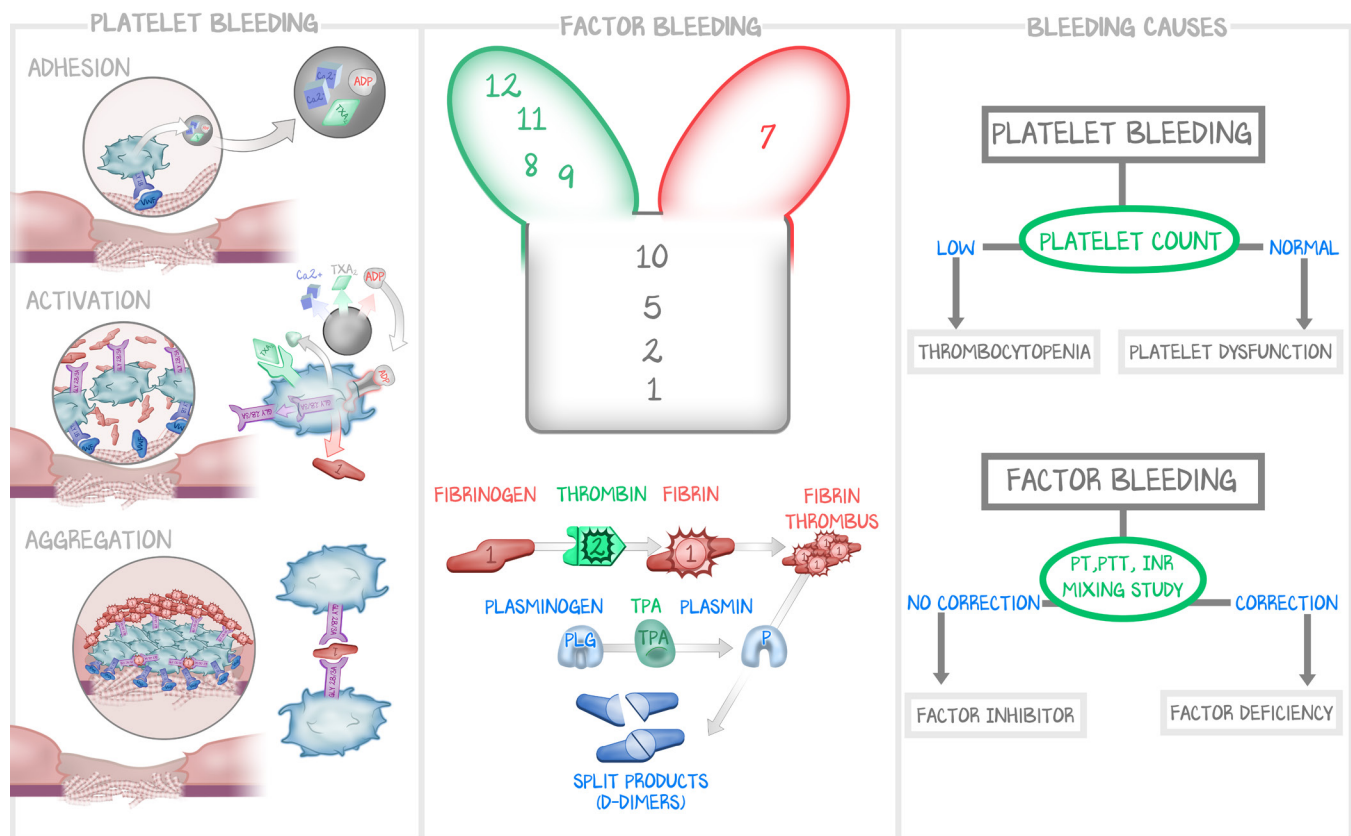


Figure 2.5: Clotting and Bleeding

Interpretation of bleeding comes down to platelet bleeding or factor bleeding. Platelet bleeding is further separated into functional dysfunctions and disorders of platelet number. Factor bleeding is evaluated with INR and a mixing study. These processes will have become innate by the end of the course. This is merely a preview.

The PT and INR are the same thing. You need not report them both. They measure the extrinsic pathway and the common pathway. The INR cannot go below 1. The reported INR is how many times above normal the person is. An INR of 2.5 is 2.5 times more anticoagulated. An INR of 10 is drastically anticoagulated. If you see an INR > 5.0, then hold the medication that is causing it; INR > 10 without bleeding can receive vitamin K; and an INR of anything with active hemorrhage needs FFP. This is discussed in Clotting #5: *Factor Bleeding*. The PTT measures the intrinsic pathway and common pathway. Elevations in the PTT are seen in heparin administration. Isolated elevations of the PTT can also be treated with FFP (which has all clotting factors), but is usually associated with a specific factor deficiency of that patient. Further workup includes the mixing study and levels for factors suspected to be deficient.

Thrombophilia is evaluated for specific conditions; one does not make a diagnosis by proving an elevated factor number.